Prognostic Significance of Surgical-Pathologic N1 Lymph Node Involvement in Non-Small Cell Lung Cancer

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Background. Patients with N1 non-small cell lung cancer represent a heterogeneous population with varying long-term survival. To better define the importance of N1 disease and its subgroups in non-small cell lung cancer staging, we analyzed patients with N1 disease using the sixth edition and proposed seventh edition TNM classifications.

Methods. From January 1995 to November 2006, 540 patients with N1 non-small cell lung cancer who had at least lobectomy with systematic mediastinal lymphadenectomy were analyzed retrospectively.

Results. For completely resected patients, the median survival rate and 5-year survival rate were 63 months and 50.3%, respectively. The 5-year survival rates for patients with hilar N1 (station 10), interlobar (station 11), and peripheral N1 (stations 12 to 14) involvement were 39%, 51%, and 53%, respectively. Patients with hilar lymph node metastasis showed a shorter survival period than patients with peripheral lymph node involvement ($p = 0.02$). Patients with hilar zone N1 (stations 10 and 11) involvement tended to show poorer survival than patients with peripheral zone N1 (12 to 14) metastasis ($p = 0.08$). Multiple-station lymph node metastasis indicated a poorer prognosis than single-station involvement (5-year survival 39% versus 51%, respectively, $p = 0.01$). Patients with multiple-zone N1 involvement showed poorer survival than patients with single-zone N1 metastasis ($p = 0.04$). A significant survival difference was observed between N1 patients with T1a versus T1b tumors ($p = 0.02$). Multivariate analysis revealed that only multiple-station lymph node metastasis was predictive of poor prognosis ($p = 0.05$).

Conclusions. Multiple-station versus single-station N1 disease and multiple-zone versus single-zone N1 involvement indicate poorer survival rate. Patients with hilar lymph node involvement had lower survival rates than patients with peripheral N1. The impact of T factor seemed to be veiled by the heterogenous nature of N1 disease. Further studies of adjusted postoperative strategies for different N1 subgroups are warranted.

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Staging of non-small cell lung cancer (NSCLC), which relies on nodal descriptors [1, 2], is important in planning surgical and nonsurgical treatment. Defining the anatomical extent of each nodal station is essential for the accurate categorization of nodal status, which serves as a basis for stage groupings [1, 2]. Stage N1 disease represents a heterogeneous group within NSCLC patients with varying 5-year survival rates. The reported 5-year survival rates of N1 patients (any T stage) vary between 27% and 67% [2–15]. The forthcoming (seventh) edition of the TNM classification proposed by the International Association for the Study of Lung Cancer (IASLC) includes a calculated rate of 34% [2]. Correct staging of lymph node metastasis in potentially resectable stage I to IIIA NSCLC influences decisions about the appropriateness and timing of surgery and adjuvant treatment [1, 2].

To provide more accurate prognostic stratification, previous studies have recommended subdividing N1 disease according to specific anatomical locations (e.g., N1 peribronchial versus N1 perihilar) or the number of involved lymph nodes (e.g., single versus multiple N1 nodes [1–15]). We analyzed the prognostic significance and characteristics of lymph node involvement in patients with surgical-pathologic N1 NSCLC using the current sixth edition and forthcoming seventh edition of the TNM classification systems.

Patients and Methods

From January 1995 to November 2006, we performed 1,616 anatomic resections in patients with NSCLC in our institution. Patients were grouped according to highest level of involved lymph node station. Of these, 862 patients (53.3%) had no nodal metastases (N0 disease),

540 (33.4%) had N1 nodal metastases (N1 disease), and 214 (13.2%) had mediastinal nodal metastases (N2 disease). We performed retrospective analysis of the pattern of lymph node metastasis and prognosis in 540 consecutive pathologic (p) N1 NSCLC patients who underwent resection. Exclusion criteria were as follows: mediastinal nodal tumor involvement; neoadjuvant therapy; resection smaller than lobectomy; multiple lung tumors; evidence of intrathoracic M1 disease at thoracotomy; and low-grade malignancy, such as bronchial carcinoid tumors. Our Institutional Review Board waived the requirement for individual patient consent.

The pathologic N1 NSCLC patients in this study included 519 men and 21 women with a median age of 57.5 ± 9.3 years (range, 30 to 79). A total of 285 patients (52.7%) had NSCLC on the right side, whereas 255 patients (47.3%) had tumors on the left side.

The preoperative workup included routine blood tests, posteroanterior and lateral chest radiographs, bronchoscopy, basic pulmonary function tests with or without diffusion capacity of lung for carbon monoxide (DLCO) and ventilation-perfusion lung scan (V/Q), and blood gas analysis. Computed tomography scans of the thorax, abdomen (or abdominal ultrasonography), and cranium (or cranial magnetic resonance imaging), and whole-body bone scintigraphy were performed in most patients for pretreatment staging. Positron emission tomography–computed tomography analysis was performed in 49 patients after 2003, when this technique became available.

Mediastinal lymph node sampling through cervical mediastinoscopy at stations 2, 4 (both left and right), and 7 in the recent mapping system [2] was performed in almost all patients except those with peripheral cT1N0 squamous cell carcinomas. Preoperative mediastinal exploration was supplemented by left anterior mediastinotomy or extended mediastinoscopy in patients whose tumor lay in the left upper lobe or left main bronchus and in those with enlarged anterior mediastinal or aorticopulmonary lymph nodes (i.e., stations 5 and 6). In all, 508 of 540 patients (94%) underwent mediastinoscopy. The mean number of sampled lymph node stations was 4.02 (range, 2 to 7).

The type of resection was decided based on anatomical tumor involvement. Pneumonectomy was performed in 253 patients (46.9%), sleeve lobectomy was performed in 60 patients (11.1%), bilobectomy was performed in 50 patients (9.3%), and lobectomy was performed in 177 patients (32.7%). For pneumonectomy and lobectomy, postoperative mortality rates were 6.3% (n = 16) and 4.2% (n = 12), respectively. Complete resection (R0) was defined as the removal of all detectable disease by the surgeon and histologic confirmation of tumor-free resection margins. Complete resection was achieved in 490 cases (90.7%). Patients with tumor-positive margins upon final pathology review after complete gross resection at thoracotomy were classified as having undergone incomplete resection (n = 50). A systematic mediastinal lymph-

adenectomy was performed in every patient in addition to anatomic lung resection. All patients underwent uniform staging to determine a final surgical-pathologic stage (pTNM), based on information obtained through thoracotomy and pathology examination [1]. Patients were grouped according to highest level of involved lymph node station. The mean number of lymph nodes resected and examined was 17 per patient (range, 2 to 67) for the N1 and N2 lymph node regions. In the N1 region, a mean of 9 lymph nodes (range, 2 to 37) was removed. All histologic specimens from patients were evaluated according to the World Health Organization classification [16]. Histopathologic tumor types included squamous carcinoma in 380 cases (70.4%), adenocarcinoma in 109 cases (20.2%), and other non-small cell carcinoma types in 51 cases (9.5%). For pathologic T classification of the primary tumor, we retrospectively followed the revised International System for Staging Lung Cancer of the Union Internationale Contre le Cancer [1]: 49 tumors (9.1%) satisfied the criteria for T1, 289 (53.5%) for T2, 162 (30%) for T3, and 40 (7.4%) for T4.

Lymph Node Metastases

We numbered the lymph nodes according to the Mountain-Dresler modification of the American Thoracic Society (MD-ATS) map [17]. Patients were grouped according to highest level of involved lymph node station: 58 patients (10.8%) had metastases in the hilar lymph nodes (N1h, stations 10, 10 + 11 ± 12 ± 13 ± 14 ±) as a more advanced level; 202 (37.4%) had metastases in the interlobar nodes (N1i, stations 11, 11 + 12 ± 13 ± 14 ±); and 280 (51.9%) had metastases in the peripheral intralobar nodes (N1p, stations 12, 13, and 14, 12 + 13 ± 14 ±). The N1 disease was classified as single station or multiple station. Lymph node stations were also grouped together into anatomical "zones": lymph nodes at stations 10 and
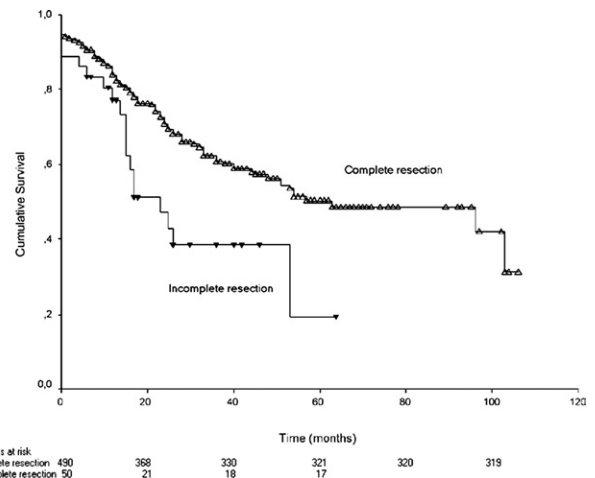

Fig 1. Patient survival according to completeness of resection.

11 were deemed to be within the hilar zone, whereas those at levels 12 to 14 were deemed to be within the peripheral zone.

Restaging According to New Staging Proposals for the TNM Classification

We retrospectively restaged completely resected (R0) 468 pN1 patients (T1, T2, or T3). The pathologic T classification of the primary tumor and N1 subgroups was determined according to the new (seventh edition) staging proposals for the TNM classification for lung cancer suggested by the IASLC [2, 18]. Lymph node involvement was classified according to anatomical zones, with 219 patients showing hilar zone involvement and 249 showing peripheral zone involvement [2]. We also subdivided N1 disease into N1a (single N1

zone) and N1b (multiple N1 zones), as suggested previously [2]. Mean follow-up time was 24.4 ± 20.8 months (range, 0 to 106).

Statistical Analyses

Patient survival was expressed by actuarial analysis according to the Kaplan-Meier method, using time zero as the date of thoracotomy and death as the endpoint. Perioperative deaths were included in survival analysis. Prognostic factors were evaluated in completely resected (R0) patients. Differences in survival were determined using the log-rank test in the univariate analysis, and prognostic factors with p values of less than 0.2 were included in the multivariate analysis using the Cox proportional hazards regression model. Results were considered significant at p less than 0.05.

Table 1. *Patient Characteristics and Prognostic Factors Revealed by Univariate Analyses in Cases With Completely Resected pN1 Non-Small Cell Carcinoma of the Lung (n = 490)*

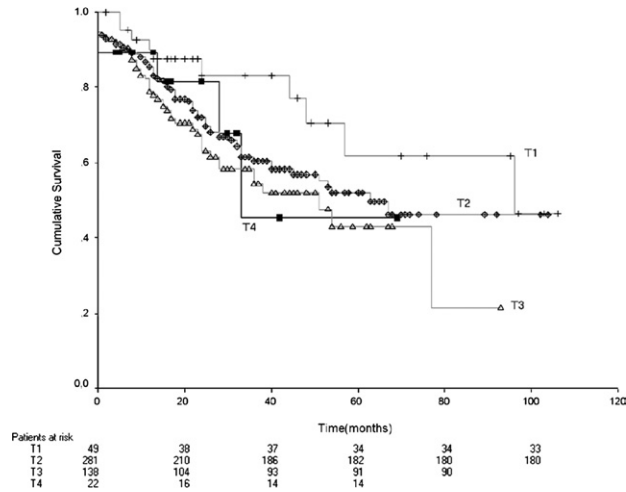|	Median Survival (Months)	5-Year Survival Rate	Comparison	Univariate p Value	Multivariate p Value	Hazard Ratio (95% CI)
Sex				0.22		
Male	63	50%				
Female	33	44%				
Site				0.64		
Right	NC	52%				
Left	54	47%				
pT classification				0.11	0.15	1.2 (0.93–1.57)
T1	96	62%				
T2	63	53%	vs. T1	0.10		
T3	51	43%	vs. T2	0.18		
T4	33	45% (3-year)	vs. T3	0.63		
Histology				0.39		
Squamous cell carcinoma	67	50%				
Adenocarcinoma	96	51%				
Others	28	43%				
Surgical procedure				0.17	0.75	0.9 (0.64–1.37)
Lobectomy	96	53%				
Pneumonectomy	53	47%				
Highest level of involved lymph node station				0.08	0.78	0.9 (0.54–1.58)
Hilar (10)	57	39%	10 versus 11	0.14		
Interlobar (11)	63	51%	11 versus 12–14	0.38		
Peripheral (12–14)	77	53%	12–14 versus 10	0.02		
Number of involved lymph node stations				0.01		
Single station	77	55%			0.05	1.7 (.0.99–2.95)
Multistation	51	39%				
Lymph node station				0.04		
10	57	39%				
11–14	77	52%				
Involved lymph node zone				0.08	0.66	0.8 (0.39–1.81)
Hilar zone (10, 11)	57	48%				
Peripheral zone (12–14)	77	53%				
Number of involved lymph node zones				0.04	0.24	0.6 (0.33–1.33)
Single zone (N1a)	67	53				
Multiple zone (N1b)	51	35				

CI = confidence interval;   NC = not calculated.

Fig 2. Patient survival curves according to T stage.

Results

The completely resected patients had a 5-year survival rate of 50.3% with a median survival time of 63 months; incompletely resected patients had a 5-year survival rate of 19% with a median survival time of 23 months ($p = 0.003$; Fig 1). The 5-year survival rates of patients with squamous cell carcinoma, adenocarcinoma, and others were 50%, 51%, and 43%, respectively. Although squamous cell carcinoma tended to show a better prognosis, no significant difference was observed among the three different histologic types ($p = 0.39$). No statistically significant difference was observed in the 5-year survival rate between right- and left-sided tumors (52% and 47%, respectively; $p = 0.64$).

The 5-year survival rates of patients with T1, T2, and T3 disease were 62%, 53%, and 43%, respectively. Patients with T4 tumors had a 3-year survival rate of 45% (Table 1, Fig 2). No significant differences in survival were found among patients with T1 and T2 ($p = 0.1$), T2 and T3 ($p = 0.18$), or T3 and T4 disease ($p = 0.63$).

Patients who underwent lobectomy had a 5-year survival rate of 53% and a median survival time of 96 months. For patients who underwent pneumonectomy, the 5-year survival rate was 47% and the median survival time was 53 months. Although patients undergoing lobectomy tended to have a better prognosis, the difference was not significant ($p = 0.17$; Fig 3).

Comparisons of survival in completely resected T1, T2, T3, and T4 NSCLC patients according to tumor histology, resection type, proposed new T status, and subgroups of N1 disease (hilar, interlobar, and peripheral) are shown in Table 2. The 5-year survival rates of patients with hilar, interlobar, and peripheral N1 were 39%, 51%, and 53%, respectively (Table 1, Fig 4). No significant difference was observed between the survival of patients with hilar and interlobar lymph node involvement ($p = 0.14$). Furthermore, no significant difference in survival was observed between patients with interlobar (station 11) and peripheral (stations 12 to 14) lymph node involvement ($p =$

0.38). However, patients with hilar lymph node (station 10) metastasis showed significantly shorter survival periods than those with peripheral (stations 12 to 14) lymph node metastasis ($p = 0.02$). In the overall study population, multiple-level lymph node metastasis was correlated with poorer prognosis compared with the involvement of a single station (5-year survival rates 39% versus 51%, $p = 0.01$; Fig 5).

Patients with hilar zone (stations 10 and 11) N1 involvement had poorer survival than patients with peripheral zone N1 (stations 12 to 14) metastasis, but the difference was not significant ($p = 0.08$; Table 1). Multiple-zone involvement showed a significantly greater influence on survival in comparison with single-zone N1 metastasis ($p = 0.04$; Table 1). Multivariate analysis showed that only multiple-station lymph node metastasis was predictive of poor prognosis ($p = 0.05$; Table 1).

When patients were restaged according to the most recently proposed TNM classification [16], we found a significant survival difference between patients with T1a and T1b tumors ($p = 0.02$). However, other T descriptions did not significantly stratify the patients (T1b versus T2a, $p = 0.85$; T2a versus T2b, $p = 0.71$; T2b versus T2c, $p = 0.81$; T2c versus T3, $p = 0.47$; Table 3). Patients with hilar (stations 10 and 11) or multiple-zone N1 (N1b) involvement showed poorer survival rates than patients with peripheral (stations 12 to 14) or single-zone N1 (N1a) metastasis ($p = 0.04$ and $p = 0.02$, respectively; Table 3).

Survival rates according to the sixth edition TNM classification and the proposed seventh edition classification using univariate and multivariate analyses are shown in Table 4.

Comment

The accurate staging of lymph node involvement is of pivotal importance in the management of NSCLC as it aids in treatment selection and predicting outcome [2]. In patients undergoing surgery for resection of NSCLC, the
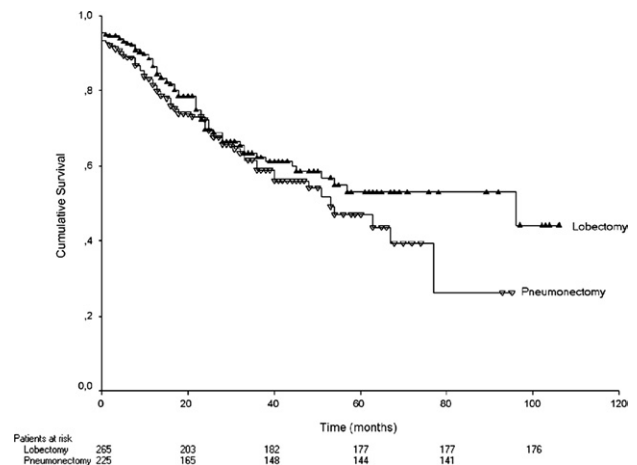

Fig 3. Survival curves for patients who underwent lobectomy or pneumonectomy.

Table 2. Distribution and Survival of Patients According to Level of N1 Nodal Involvement

	Total n = 490	Hilar (10) n = 50				Interlobar (11) n = 180				Peripheral (12–14) n = 260			
		n	Median Survival (5-Year %)	Comparison	p Value	n	Median Survival (5-Year %)	Comparison	p Value	n	Median Survival (5-Year %)	Comparison	p Value
pT classification					0.47				0.20				0.19
T1	49	5	57 (0)			22	NC (76)			22	NC (63)		
T2	280	29	67 (59)	vs. T1	0.93	86	40 (47)	vs. T1	0.05	165	NC (56)	vs. T1	0.48
T3	139	14	14 (22)	vs. T2	0.16	62	51 (29)	vs. T2	0.42	63	54 (45)	vs. T2	0.08
T4	22	2	14 (0)	vs. T3	0.72	10	NC (85)	vs. T3	0.60	10	33 (0)	vs. T3	0.88
Histology					0.6				0.13				0.94
SCC	346	38	57 (25)			128	NC (53)			180	77 (53)		
ACA	101	8	NC (72)			35	48 (48)			58	NC (50)		
Others	43	4	13 (0)			17	31 (35)			22	NC (51)		
Surgical procedure					0.31				0.10				0.78
Lobectomy	265	20	57 (40)			74	NC (70)			171	54 (49)		
Pneumonectomy	225	30	33 (46)			106	40 (35)			89	77 (58)		
Proposed T status													
T1a, x ≤ 2 cm	25	3	NC			11	NC (89)			11	78 (67)		
T1b, 2 cm < x ≤ 3 cm	24	2	NC	vs. T1a	0.31	11	96 (59)	vs. T1a	0.23	11	NC (38)	vs. T1a	0.09
T2a, 3 cm < x ≤ 5 cm	152	13	33 (49)	vs. T1b	0.54	48	40 (46)	vs. T1b	0.27	91	NC (52)	vs. T1b	0.44
T2b, 5 cm < x ≤ 7 cm	73	11	NC	vs. T2a	0.39	19	63 (72)	vs. T2a	0.67	43	NC (56)	vs. T2a	0.61
T2c, x > 7 cm	57	5	NC	vs. T2b	0.89	21	26 (25)	vs. T2b	0.28	31	NC (78)	vs. T2b	0.10
T3	137	14	14 (NC)	vs. T2c	0.29	60	51 (27)	vs. T2c	0.26	63	54 (45)	vs. T2c	0.04
T4	22	2	14 (0)	vs. T3	0.72	10	NC (85)	vs. T3	0.60	10	33 (0)	vs. T3	0.88

ACA = adenocarcinoma;   NC = not calculated;   SCC = squamous cell carcinoma;   x = tumor size.
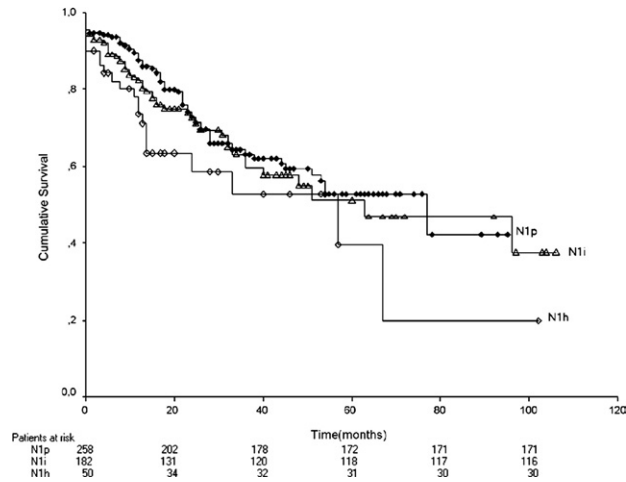
Fig 4. Overall survival according to N1 lymph node metastasis for patients with hilar N1 (station 10), interlobar N1 (station 11), or peripheral N1 (stations 12 to 14).

assessment of nodal disease has gradually become an accepted part of the operation [2].

The latest revisions of the TNM staging system were adopted in 1997 [1]. These consisted of stage grouping by a recombination of T, N, and M factors, and redefinition of these factors. In the 1987 version of the TNM staging system, N1 tumors were categorized into two stage groups for T1 to T3 tumors without distant disease: stage II (T1N1, T2N1) and stage IIIA (T3N1) [25]. As a result of the TNM recombination in the 1997 revision, these tumors were divided into three stage groups: stage IIA (T1N1), stage IIB (T2N1), and stage IIIA (T3N1). However, the changes in TNM descriptors were limited to defining tumors with satellite nodules in the same lobe as the primary tumor as T4, while the definitions of N and M factors remained unchanged [17].

Accurate staging is based on the accurate definition of TNM descriptors. The number of N1 cases analyzed for the fifth TNM staging was 419 [7]. The seventh staging proposal was based on 2,538 N1 and N2 patients for whom data regarding primary tumors in relation to the presence of lymph node metastases were available. In practice, this proposed stage classification system identified 5,770 of 67,725 NSCLC patients (8.5%) as having N1and N2 disease, leading to questions of selection bias [2, 18, 19]. Furthermore, Information on the site of the primary tumor in relationship to the presence of lymph node metastases (pN) was available from 2,538 N1 and N2 cases, and only 522 N1 (0.8%) cases with involvement of peribronchial levels 12 to 14 were evaluated to determine whether survival was influenced [2] by involvement of the peribronchial (levels 12 to 14) versus the interlobar (level 11) or hilar (level 10) lymph nodes, or by combinations of these. For this reason, selection bias should be eliminated as much as possible to make more realistic classification according to N1 involvement. In addition, the number of N1 patients may be suboptimal to perform subgroup analysis in N1 patients (i.e., single-station N1, multiple-station N1, multiple-zone N1, and so forth).

To better define the importance of N1 disease and its subgroups in NSCLC staging, we analyzed patients with N1 disease according to the current sixth and proposed seventh classification systems. As one conclusion of the proposed seventh edition, current N descriptors should be maintained in the NSCLC staging system [2].

A number of studies have reported the patterns of lymphatic drainage of the lung and have evaluated the role of N1 lymph node involvement in survival. These series were retrospective and included relatively small numbers of patients, and they usually reported the subgroups of N1 disease (i.e., hilar, interlobar, and intersegmental lymph nodes; Table 5) [2–15]. The reported 5-year overall survival rates of patients (any T stage) with N1 disease vary between 27.2% and 67%, according to the stage of disease (Table 5) [2–15]. Mountain [1] reported that patients with stage IIA pT1N1 disease had a 5-year survival rate of 55%, whereas patients with stage IIB pT2 N1, stage IIIA pT3 N1, and stage IIIB pT4 N1 disease had rates of 39%, 25%, and 8%, respectively. The forthcoming seventh edition of the TNM classification proposal for lung cancer reports a median survival period of 34 months and 5-year survival rate of 38% among patients with surgical-pathologic N1 disease [2]. In our series, the median survival period was 63 months and the 5-year survival rate was 50.3%.

The number of involved lymph node nodules or stations and the involved station level are decisive factors for postoperative survival in N1 disease. Some studies indicated that hilar lymph node involvement is a poor prognostic indicator compared with interlobar or lobar lymph node involvement [6, 10, 13, 18], whereas other studies found no significant differences [15, 20, 21]. A number of studies suggested that patients with hilar node involvement had a poorer prognosis than patients with interlobar or peribronchial lymph node metastasis (Table 5) [2]. The hilar lymph nodes are contiguous with the lobar lymph nodes distally and also with the mediastinal lymph nodes proximally. Conversely, multiple lymph node nodule or station involvement was reported
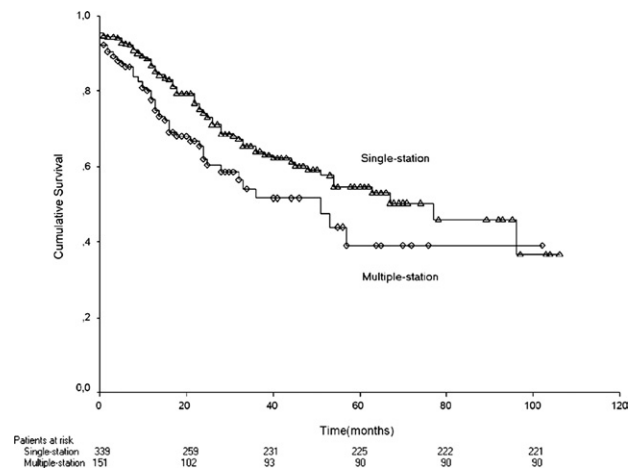

Fig 5. Overall survival of patients with single-station Nl or multiple-station N1 involvement.

Table 3. Completely Resected Non-Small Cell Lung Cancer Patients Staged According to New (Seventh Edition) Proposed Staging System

	n = 468	Median (Months)	1-Year (%)	3-Year (%)	5-Year (%)	Comparison	Univariate p Value	Multivariate p Value	Hazard Ratio (95% CI)
New T status							0.99	0.22	
T1a, x ≤ 2 cm	25	NC	95	95	82				
T1b, 2 cm < x ≤ 3 cm	24	57	85	65	35	vs. T1a	0.02	0.02	0.1 (0.04–0.7)
T2a, 3 cm < x ≤ 5 cm	153	54	85	60	46	vs. T1b	0.85	0.98	0.9 (0.4–2.1)
T2b, 5 cm < x ≤ 7 cm	71	NC	81	65	60	vs. T2a	0.71	0.38	0.8 (0.5–1.2)
T2c, x > 7 cm	57		91	51	51	vs. T2b	0.81	0.16	0.6 (0.3–1.1)
T3	138	51	78	54	42	vs. T2c	0.30	0.47	0.7 (0.4–1.5)
New N1 descriptors									
Involved lymph node zone									
Hilar zone (10,11)	219	57	79	60	47				
Peripheral zone (12,13,14)	249	77	90	65	54	vs. Hilar zone	0.04	0.14	1.4 (0.8–2.1)
Number of involved lymph node zones									
Single zone (N1a)	367	67	86	63	54				
Multiple zone (N1b)	101	51	75	52	35	vs. N1a	0.02	0.87	0.9 (0.5–1.6)

CI = confidence interval;   NC = not calculated;   x = tumor size.

to be a poor prognostic factor in comparison with single involvement [6, 20, 22], whereas other studies did not show any significant association between prognosis and the number of involved lymph node nodules or stations [13–15]. Therefore, the clinical implications of the degree of lymph node involvement in N1 disease remain unclear. In the new staging proposal, differences in outcome could not be identified for patients with peripheral versus hilar N1 disease [2].

In our study, the survival of patients with hilar disease did not differ significantly from that of patients with interlobar N1 disease. Similarly, peripheral and interlobar N1 disease did not differ in terms of patient survival. However, patients with hilar lymph node positivity had significantly poorer survival than did patients with peripheral N1 involvement ($p = 0.02$).

Discrepancies in the results of this and other studies may be partly attributable to interindividual differences in determining the borders between the anatomic locations of the lymph node stations, especially for the hilar lymph nodes. Watanabe and colleagues [23] studied the interobserver variability in systematic lymph node dis-

section and reported that the concordance rate for N1 stations was only 72.3% between two observers from Japan and the United Kingdom. The Naruke map [24, 25] designates lymph nodes in the subcarinal space along the inferior border of the main stem bronchus to be station 10, whereas these are classified as level 7 (i.e., N2) in the MD-ATS map [17]. In our study, the patients were staged according to the MD-ATS map [17], and therefore it is fair to assume that our lymph node dissection and mapping system were homogenous.

We found that survival was significantly poorer in cases with multiple-level versus single-level N1 nodal metastases. Martini and colleagues [7] proposed that the number of involved N1 nodes is a significant prognostic factor. However, Asamura and colleagues [12] reported no difference in survival between patients with single- and multiple-station N1 metastases.

The most remarkable finding with respect to pN staging in the IASLC database is that patients fall into two prognostically distinct N1 categories depending on the extent of nodal metastases: single-zone N1 or multiple-zone N1 [2]. These results suggest that the tumoral

Table 4. Univariate and Multivariate Analyses of Patients According to Sixth Edition (6th) TNM and Pathologic Stage Groupings According to Seventh Edition (7th) IASLC Proposed

Stage	Median Survival (Months)		1-Year (%)		3-Year (%)		5-Year (%)		Comparison	Univariate p Value		Multivariate p Value	Hazard Ratio (95% CI)	Multivariate p Value	Hazard Ratio (95% CI)
	6th	7th	6th	7th	6th	7th	6th	7th		6th	7th	6th	6th	7th	7th
IIA	96	57	90	87	82	65	58	49				0.28		0.38	
IIB	63	NC	85	81	61	65	52	60	vs. IIA	0.16	0.99	0.36	1.3 (0.6–2.6)	0.66	0.8 (0.5–1.5)
IIIA	51	51	78	82	54	54	43	46	vs. IIB	0.15	0.42	0.10	1.8 (0.8–3.6)	0.28	1.2 (0.8–1.8)
IIIB	33		89		49		—		vs. IIA	0.6		0.94	1.0 (0.2–3.8)		

CI = confidence interval;   IASLC = International Association for the Study of Lung Cancer.

Table 5. Results of Series Reporting Outcome of Patients With N1 Disease Undergoing Resection for Non-Small Cell Lung Cancer

First Author [Reference]	Patient No.	T Stage	Five-Year Survival (%)			
			Overall	Hilar Metastasis	Interlobar Metastasis	Peripheral Metastasis
Maggi, 1990 [3]	157	T1–T4	46.1	NS	NS	NS
Martini, 1992 [4]	214	T1–T2	39	NS	NS	NS
Yano, 1994 [5]	78	T1–T3	49.2	39.7[a]		64.5
van Velzen, 1996 [6]	57	T1	45.7	23.3[a]		55.6
van Velzen, 1997 [7]	369	T2	37.8	30.3[a]		57.3
van Velzen, 1999 [8]	111	T3–T4	27.2	NS	NS	NS
Sawyer, 1999 [9]	107	T1–T4	32	NS	NS	NS
Riquet, 1999 [10]	256	T1–T4	47.5	38.5[a]		52.6
Yoshino, 1999 [11]	43	T1–T2	50.2	47.4[a]		55
Asamura, 2000 [12]	180	T1–T4	67	54	70[b]	
Tanaka, 2001 [13]	95	T1–T2	58	39	62 66[b]	72
Marra, 2003 [14]	535	T1–T4	40	30	39	
Nakagawa, 2007 [15]	85	T1–T2	54	52	54	56
Rush/IASLC 2007 [2]	5716	T1–T4	38	NS	NS	NS
Our series	490	T1–T4	50.3	39	51	53
	490	T1–T4	50.3	48[a]		53
	490	T1–T4	50.3	39	52[b]	

[a] Hilar and interlobar patients were analyzed as a single group.

[b] Interlobar and peripheral patients were analyzed as a single group.

NS = not shown.

burden involving the lymph nodes, rather than just the anatomic location of lymph node involvement, may have the most significant influence on survival. These three classes of lymph node metastasis have not been clearly identified in previous reports, which focused predominantly on comparing survival relative to varying levels of either N1 or N2 disease. Validation of the proposed differences in N descriptors for the staging system would clearly require a prospective study in even larger numbers of patients with meticulous pN staging [2]. In the present study, multiple-zone N1 disease showed a significantly different prognosis ($p = 0.04$). However, without zone construction, multiple-station N1 disease showed a significantly poorer survival rate than single-station N1 disease ($p = 0.01$). Nevertheless, our results provide the impetus for a prospective study to clarify this issue.

In pN1 cases, the decision to perform pneumonectomy or simply sleeve resection, bilobectomy, or lobectomy is often difficult. Involvement of these nodes implies that tumor cells have entered the lymphatic channels of the adjacent lobe, and pneumonectomy may be required to obtain complete resection [26, 27]. However, pneumonectomy involves a higher incidence of postoperative complications, poor quality of life, cardiopulmonary dysfunction, and long-term complications [28, 29]. Although our patients undergoing lobectomy tended to have a better prognosis, this effect was not significant ($p = 0.17$). When metastatic nodes are encapsulated and removed completely, lobectomy should be preferred even if the metastatic node is located extralobally.

In most previous studies, T factor was not a significant prognostic indicator in patients with N1 disease [4, 5, 7–11, 13–15, 30, 31]. However, T classification along with the level of N1 involvement clearly showed statistical power in one study [14]. Among patients with N1 disease in our study, the T factor (T1 to 3) did not show statistically significant survival stratification according to the sixth NSCLC staging system (Table 1). However, according to the seventh staging proposal, only patients with T1a and T2b tumors had significantly different survival rates (Table 2). This may be attributable to the marked heterogeneity of N1 disease (i.e., single-station N1, multiple-zone N1, or multiple-station N1) or to the relatively small number of patients with T1 tumors.

There were a number of limitations to our study. First, we did not analyze N2 patients along with those showing N1 involvement. Second, we were not able investigate the role of adjuvant therapy, as adjuvant therapy protocols varied greatly during the study period. However, this heterogeneity is unlikely to have caused bias in our series, as administration of adjuvant therapy did not accumulate for any specific time period or group of patients.

In conclusion, among NSCLC patients with N1 disease, those with hilar lymph node involvement showed the poorest survival rate in comparison with patients who had peripheral (stations 12 to 14) lymph node involvement. Multiple-station and multiple-zone N1 tumor involvement represents a subgroup of N1 patients who have an extremely poor prognosis. In addition, the proposed subclassification of T1 patients into T1a and T1b

groups seemed justified based on our series. However, subclassification of T2 tumors was not supported in our series, and further studies are required to investigate this issue. Further analyses using larger numbers of patients with N1 disease along with patients with N0 and N2 disease from additional centers are necessary.

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